REMARKS

Claims 19 to 56 are pending in the application, of which claims 19 to 24, 29, 30, 42, and 43 are currently under consideration. Claim 19 has been amended. The amendment to claim 19 is supported throughout the specification, *e.g.*, at page 7, lines 9 to 11; at page 11, lines 8 to 13; and elsewhere.

The specification has been amended at page 10 to include the ATCC accession number and date of deposit for hybridoma line HB 12078. The specification has also been amended at page 10 to reflect the current address of the American Type Culture Collection. The specification has been amended at page 13 to replace the word "Doman" with the word "Domain," solely to correct a typographic error.

Those amendments add no new matter.

ELECTION

Applicants note the Examiner's acknowledgement of the election of Group II, claims 19, 29, 30, 42, and 43 without traverse. Applicants thank the Examiner for rejoining claims 20 to 24.

OBJECTION

The Examiner objected to the specification for allegedly failing to comply with the sequence rules. Action at page 2. Specifically, the Examiner alleged that "no sequence identifier is associated with the sequences disclosed on pages 13-16." *Id.* The Examiner included a Notice To Comply With Requirements For Patent Applications

Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures ("Notice") with the Office Action. A copy of the Notice is enclosed with this Amendment and Response.

Applicants respectfully traverse. Applicants filed an Amendment and Response to a Notice to File Corrected Application Papers on February 6, 2002. In that Amendment and Response, Applicants amended the specification to include SEQ ID NOs on pages 13 to 16. Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Written Description

The Examiner rejected claims 24, 42, and 43 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Action at page 3. The Examiner alleged that "[a]mendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit." *Id.*

Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended the specification to include both the date of deposit for HB 12078 and the current address for the American Type Culture Collection ("ATCC"). Applicants also enclose a copy of the ATCC Deposit Receipt, indicating that hybridoma line HB 12078 was deposited on April 4, 1996. That Receipt also states that "[t]he

strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain." Those amendments and the Deposit Receipt should obviate the Examiner's rejection.

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 24, 42, and 43 under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 19 to 23, 29, and 30 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Action at page 5. The Examiner stated that "[t]he specification teaches monoclonal antibody mAb74 (produced by the hybridoma ATCC No. HB 12078), wherein the treatment of Her2 expressing cells with the antibody resulted in apoptosis." *Id.* The Examiner then alleged that "[t]he specification does not disclose any other monoclonal antibodies or fragments thereof inducing apoptosis as broadly encompassed in the claim." *Id.* The Examiner alleged that "[i]n this case, the only factor present in the claim is a recitation of an antibody or fragment thereof." *Id.* The Examiner further alleged that "the specification does not directly describe the antibodies useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards." Action at page 8. The Examiner alleged that

> the instant specification may provide an adequate written description of an antibody or fragment thereof, per Lilly by structurally describing representative polypeptides or by describing "structural features common to the members of the genus, which features constitute a substantial

> portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination off such characteristics."

Id.

Applicants respectively traverse. Solely to expedite prosecution and without acquiescing to the rejections, Applicants have amended claim 19 to recite: "[a] method for treating cancer characterized by overexpression of Her2, in a patient, comprising administering an antibody or fragment thereof that binds to Her2 and induces apoptosis in Her2 overexpressing cells." Claims 20 to 23, 29, and 30 depend from claim 19.

As the Examiner confirmed, the court in Enzo noted with approval the U.S. Patent and Trademark Office's (USPTO's) Guidelines for compliance with the written description requirement, stating that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" 296 F.3d 1316, 1324 (Fed. Cir. 2002) (citing Guidelines, 66 Fed. Reg. at 1106). The court also noted with approval the specific example in the USPTO's Synopsis of Application of Written Description Guidelines (Synopsis) that addressed sufficient written description of antibodies:

> the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional

> characteristics of antibody binding, and the fact that the antibody technology is well developed and mature."

Id (citing Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm). Thus, Applicants assert that the written description requirement is satisfied for an antibody even without disclosing specific antibody structure or additional function beyond the ability to bind an antigen.

The present specification describes antibodies that bind to Her2 throughout, *e.g.*, at page 7, lines 9 to 11. The present claims additionally recite that the antibody or fragment thereof that binds Her2 "induces apoptosis in Her2 overexpressing cells." Such antibodies that induce apoptosis in Her2 overexpressing cells are described throughout the specification, *e.g.*, at page 4, lines 23 to 24. Thus, the recited antibodies are described by both the ability to bind to a specific antigen, which is sufficient description of the antibody according to the USPTO's Synopsis, as well as the ability to induce apoptosis in Her2 overexpressing cells. Thus, Applicants assert that the specification adequately describes the antibodies recited in the present claims.

Applicants respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph.

Enablement

The Examiner rejected claims 19 to 24, 29, 30, 42, and 43 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Action at page 9. Specifically, the Examiner alleged that "the specification, while being enabling for a method for treating cancer comprising administering mAb74 or fragment thereof to induce apoptosis in Her2

overexpressing cells in cell culture (*in vitro*), does not reasonably provide enablement for a method for treating cancer in a patient comprising administering an antibody or fragment thereof to induce apoptosis in Her2 overexpressing cells *in vivo*." *Id.* The Examiner then alleged that

> one cannot extrapolate the teaching of the specification to the scope of the claims because the specification makes it clear that the finding of an antibody that induces apoptosis is an unexpected event. An unexpected event is, by its nature, unpredictable.

Action at page 10. The Examiner further alleged that:

> screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, (Fed Cir., 2004) that screening assays, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Id.

Applicants traverse. Solely to expedite prosecution and without acquiescing to the rejections, Applicants have amended claim 19 to recite: "[a] method for treating cancer characterized by overexpression of Her2, in a patient, comprising administering an antibody or fragment thereof that binds to Her2 and induces apoptosis in Her2 overexpressing cells." Claims 20 to 23, 29, 30, 42, and 43 depend from claim 19.

As an initial matter, Applicants assert that whether or not the specification "makes it clear that the finding of an antibody that induces apoptosis is an unexpected event," as the Examiner contends, is irrelevant to an enablement inquiry. The enablement inquiry is unconcerned with expectations.

Furthermore, predictability alone is <u>not</u> the standard for enablement. Rather, the standard for enablement is whether one skilled in the art could practice the claimed

invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Experimentation is permissible so long as it is not undue. *Id.*

Applicants assert that the specification enables a person skilled in the art to practice the claimed method without undue experimentation. For example, the specification teaches how to make an antibody or fragment thereof that binds to Her2 , e.g, at Example 2. The specification teaches how to select an antibody that induces apoptosis in Her2 overexpressing cells, *e.g.*, at Example 6. The specification teaches how to make pharmaceutical compositions comprising an antibody or fragment thereof that binds Her2 and induces apoptosis in Her2 overexpressing cells, *e.g.*, at page 12, lines 3 to 14. The specification also teaches certain routes of administration for such pharmaceutical compositions, *e.g.*, at page 11, lines 29 to 33.

The Examiner cited *Rochester* for alleged support of the contention that "screening assays do not enable the claimed invention." Action at page 10. *Rochester,* however, addressed the screening of chemical compounds, not the selection of antibodies. A more pertinent discussion for the present claims is included in *In re Wands*, which directly addressed enablement of antibodies. *See* 858 F.2d 731 (Fed. Cir. 1988).

In *Wands*, the court concluded that, in view of the appellant's specification, obtaining antibodies needed to practice the claimed invention would not require undue experimentation. *Id.* at 740. The court stated that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics." *Id.* at 740. Furthermore, "[t]he test is not merely

quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Id.* at 737. Thus, following *Wands*, one must conclude that it is not undue experimentation for one skilled in the art to make antibodies to Her2 and select those with desired characteristics, *i.e.*, antibodies that bind to Her2 and induce apoptosis in Her2 overexpressing cells. The antibodies recited in the present claims are therefore enabled by the specification.

The Examiner also alleged that "[t]he greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability." Action at pages 10 to 11.

Applicants respectfully traverse. As an initial matter, Applicants assert that predictability alone is not the standard for enablement. Rather, the standard for enablement is whether one skilled in the art could practice the claimed invention without undue experimentation. *See Wands*, 858 F.2d 731 (Fed. Cir. 1988). Applicants assert that the specification enables the present claims for at least the reasons discussed herein.

The Examiner cited numerous documents to try to support certain aspects of the Examiner's contentions. Applicants will address each of the documents in turn below.

Freshney, Dermer, & Drexler

The Examiner alleged that "cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type." Action at page 11.

To try to support that contention, the Examiner cited Freshney, CULTURE OF ANIMAL CELLS, A MANUAL OF BASIC TECHNIQUE, Alan R. Liss, Inc., New York (1983) ("*Freshney*"), Dermer, *Bio/Technology* Vol. 12 March 1994, 320 ("*Dermer*"), and Drexler, *Leukemia & Lymphoma,* 9:1-25 (1993) ("*Drexler*"). Action at pages 11 to 12.

The Examiner alleged that *Freshney* teaches that "tissue culture [is] regarded in a rather skeptical light." Action at page 11. The Examiner, however, has taken the author's statements out of context. The entire quote from Freshney follows:

> It is not difficult to find many more differences between the environmental conditions of a cell in vitro and in vivo and this has often led to tissue culture being regarded in a rather skeptical light. Although the existence of such differences cannot be denied, it must be emphasized that many specialized functions are expressed in culture and as long as the limits of the model are appreciated, it can be a very valuable tool.

Freshney at page 4, right column, second full paragraph (emphasis added). Thus, rather than endorsing the skeptical view of cell culture articulated by others, Freshney emphasizes the value of cell culture models such as those used in the present specification.

The Examiner alleged that *Dermer* teaches that "'petri dish cancer' is a poor representation of malignancy with characteristics profoundly different from the human disease." Action at page 11. Applicants note that this criticism in *Dermer* was directed at "[d]ata from undifferentiated, ageless 'normal' cell lines – like 3T3 in which the pathways that are struck by cancer, those of development and aging, are absent." *Dermer* at left column, fifth paragraph. *Dermer* in fact urges the use of "models that mimic the human body and the developmental pathways of human cells, both normal and malignant." *Id.* at right column, third full paragraph. Applicants assert that the cells

used for the apoptosis assays in the present application, *e.g.,* the MCF7, SKBR3, and MDAMB 453 cell lines, are just such cells, i.e., those that mimic malignant human cells. The MCF7, SKBR3, and MDAMB 453 cell lines are all members of a group of cell lines (referred to as the "NCI-60 Panel") that were developed by the National Cancer Institute for the explicit purpose of identifying compounds with anti-cancer activity. *See* Screening Services, DTP Human Tumor Cell Line Screen, *available at* http://dtp.nci.nih.gov/branches/btb/ivclsp.html (a copy of which is enclosed); *see also* Cell Lines in the In Vitro Screen, *available at* http://dtp.nci.nih.gov/docs/misc/common_files/cell_list.html (a copy of which is enclosed). The National Cancer Institute has therefore not only recognized the value of using cell lines to identify anti-cancer therapeutic molecules, but has endorsed the specific cell lines used in the present application.

Furthermore, anti-cancer results obtained using the cell lines in the NCI-60 Panel were demonstrated to be reasonably correlated to Phase II clinical trial results in Voskoglou-Nomikos et al., *Clinical Cancer Research* 9:4227-4239 (2003) ("*Voskoglou-Nomikos*"). See *Voskoglou-Nomikos*, a copy of which is enclosed, at Abstract. Therefore, Applicants assert that, contrary to the Examiner's contentions, the cell lines used in the present specification are suitable models for *in vivo* activity. Furthermore, following *Voskoglou-Nomikos*, it is reasonable to extrapolate the *in vitro* results obtained using those cell lines to the results a person skilled in the art would obtain using the *in vivo* method of the present claims. Thus, Applicants assert that the specification enables the claimed method.

The Examiner alleged that *Drexler* teaches, "in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded." Action at page 12. Applicants assert that the observations made in *Drexler*'s study of Hodgkin and Reed-Sternberg cancer cell lines should not be applied to the particular cell lines used in the present specification. As discussed above, the cell lines used in the present specification to demonstrate the induction of apoptosis by an antibody or fragment thereof that binds to Her2 are on the NCI-60 Panel of cell lines that have been identified as particularly valuable for the identification of anti-cancer therapeutic molecules. None of the cell lines discussed in *Drexler* is on the NCI-60 Panel.

Furthermore, *Drexler* notes that the development of Hodgkin and Reed-Sternberg cell lines has been particularly difficult relative to the development of other types of cancer cell lines. See *Drexler* at Abstract. Thus, for at least those reasons, Applicants assert that the conclusions in *Drexler* are inapplicable to the cell lines used to demonstrate the apoptotic activity in the present specification. Moreover, as discussed above, *Voskoglou-Nomikos* showed that the anti-cancer results obtained using cell lines on the NCI-60 Panel reasonably correlate to the results of Phase II clinical trials. Applicants therefore assert that, contrary to the Examiner's contentions, *in vitro* tumor cell lines can be valuable and accurate tools for the discovery and development of cancer therapeutics. Therefore, Applicants assert that *Drexler* does not support a finding of nonenablement.

Gura, Jain, & Curti

The Examiner alleged that "[b]ecause of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion any antibody or HER2 antibody could be predictably used as an anti-cancer agent for cancer therapeutic strategies as inferred by the claim and as contemplated by the specification." Action at page 12. The Examiner cited Gura, *Science*, 273:1041-42 (1997) ("*Gura*"), Jain, *Scientific American*, pages 58-65, July 1994 ("*Jain*"), and Curti, *Critical Reviews in Oncology/Hematology*, 14:29-39 (1993) ("*Curti*"), in support of that contention.

As an initial matter, as discussed above, Applicants assert that predictability alone is not the standard for enablement. The standard for enablement is whether one skilled in the art could practice the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants assert that the present claims are enabled according to the appropriate standard.

The Examiner alleged that *Gura* teaches that "researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile." Action at page 12. *Gura* focuses, however, on the drawbacks of non-human cell lines and animal models for identifying anti-cancer drugs, and not on the NCI-60 Panel, of which the cell lines used in the present application are members. In fact, *Gura* discusses the NCI-60 Panel briefly, stating that "the limitations of animal models have spurred the NCI, among others, to test drug candidates in cultures of human cells. The institute now relies on a panel of 60 human tumor cell

lines . . . ." *Gura* at page 1042, left column, second full paragraph (emphasis added). Applicants assert, therefore, that *Gura* supports the usefulness of those cell lines in the development of anti-cancer therapeutics. In addition, *Voskoglou-Nomikos*, as discussed above, has demonstrated the correlation between efficacy of therapeutics in the NCI-60 Panel and efficacy in Phase II clinical trials. Therefore, contrary to the Examiner's contention, the *in vitro* results in the present application are a reasonable indication of the *in vivo* efficacy of the recited antibodies. Applicants assert that *Gura* supports that conclusion.

The Examiner alleged that *Jain* teaches that "tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p.65, col. 3)." Action at pages 12 and 13. Applicants assert that *Jain* focuses on the problems of chemical therapeutics, and not antibody therapeutics. Many chemical therapeutics are also toxic to normal cells and therefore cannot be used at high doses. See, *e.g.*, *Jain* at page 58, center column, second full paragraph. *Jain* does address administering antibodies to patients, however, in the context of using antibodies specific for cancer cells to aid in the efficacy of chemical therapeutics. *Jain* at page 64, right column, first full paragraph. *Jain* notes that high doses of antibodies can be used without harming normal tissue. *Id.* That proposal implies that antibodies are able to reach tumors effectively, and therefore suggests that antibodies themselves would be appropriate for use as anti-tumor agents. Thus, *Jain* actually helps to support the conclusion that the present claims are enabled.

The Examiner alleged that *Curti* teaches that "solid tumors resist destruction by chemotherapy agents." Action at page 13. The resistance mechanisms discussed in *Curti,* however, include "p170 glycoprotein-mediated resistance to anthracycline and vinca alkaloid classes of chemotherapy drugs and upregulation of thymidylate synthase leading to 5'-fluorouracil resistance." Curti at page 29, Introduction. Applicants assert that those resistance mechanisms are applicable to chemotherapeutics, and not to antibody therapeutics, as recited in the present claims. Moreover, the Examiner has not demonstrated that any of the resistance mechanisms discussed in *Curti* would affect an antibody therapeutic. Therefore, *Curti* is not applicable to the question of whether the present claims are enabled.

The Examiner finally alleged that ". . . no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as inferred and contemplated by the specification with a reasonable expectation of success." *Id* at page 14.

Applicants traverse. Predictability alone is not the standard for enablement. Nor does a reasonable expectation of success enter into an enablement inquiry. Rather, the standard for enablement is whether one skilled in the art could practice the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants assert, for the reasons discussed herein, that the Examiner's contentions do not support a finding of nonenablement.

Stancovski, Lewis, U.S. Patent No. 5,677,171, & Strobel

The Examiner alleged that "it is well known in the art that it is HERCEPTIN, and not any HER2 antibody, which is postulated as a novel and attractive therapeutic strategy in patients with cancer overexpressing HER2." Action at page 14. The Examiner cited Stancovski, *Proc. Natl. Acad. Sci. U.S.A.*, 88:8691-95 (1991) ("*Stancovski*"), Lewis, *Cancer Immunol. Immunother.*, 37:255-63 (1993) ("*Lewis*"), U.S. Patent No. 5,677,171 ("the '171 patent"), and Strobel, *Gynecologic Oncology*, 73:362-67 (1999) ("*Strobel*") to try to support that contention. Action at pages 14 to 15.

Applicants traverse. As an initial matter, the success of Herceptin demonstrates that an antibody or fragment thereof that binds Her2 can be successfully used as an anti-cancer therapy. Herceptin demonstrates that the issues the Examiner has thus far raised are clearly surmounted by antibody therapeutics. Therefore, the success of Herceptin actually supports Applicants' assertion that the present claims are enabled.

The Examiner alleged that *Stancovski* teaches that "while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth." Action at page 15. The Examiner alleged that Lewis made a similar observation. *Id.* Applicants assert that the question of whether some anti-Her2 antibodies accelerate tumor growth fails to impact the enablement of the present claims . Claim 19 recites "an antibody or fragment thereof that binds to Her2 and induces apoptosis in Her2 overexpressing cells." As discussed above, Applicants assert that, using the teachings in the specification and the knowledge in the art, one skilled in the art could select an antibody or fragment thereof that binds to Her2 and

induces apoptosis in Her2 overexpressing cells without undue experimentation. Discarding some undesirable antibodies in the selection process is simply part of the experimentation permitted by *Wands*. Thus, *Stancovski* has no bearing on whether the instant claims are enabled.

The Examiner alleged that the '171 patent teaches that "not every anti-ErbB2 antibody can be used as effectively as monoclonal antibody 4D5 (col 18, lines 15-23)." Action at page 15. As discussed above, Applicants assert that one skilled in the art could make an antibody or fragment thereof that binds to Her2 and induces apoptosis in Her2 overexpressing cells using the teachings of the specification and the knowledge in the art without undue experimentation. Discarding some undesirable antibodies in the selection process is simply part of the experimentation permitted by *Wands*. Thus, the Examiner's contentions with respect to the '171 patent have no bearing on whether the present claims are enabled.

Finally, the Examiner alleged that *Strobel* teaches that, although two different antibodies were found to block ligand binding to a receptor, "only one of the antibodies could be used effectively to block cancer cell adhesion to inhibit malignancy." Action at page 15. As discussed above, Applicants assert that one skilled in the art could select an antibody or fragment thereof that binds to Her2 and induces apoptosis in Her2 overexpressing cells without undue experimentation. Again, discarding some undesirable antibodies in the selection process is simply part of the experimentation permitted by *Wands*. Accordingly, *Strobel* has no bearing on whether the present claims are enabled.

For at least the reasons discussed herein, Applicants assert that the specification enables the present claims. Applicants respectfully request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph.

Applicants assert that the application is in condition for allowance and respectfully request that the Examiner issue a timely Notice of Allowance. If the Examiner does not consider the present application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6766 to set up an interview.

Please grant any extensions of time required to enter this Amendment and Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 2, 2006

By: _____
Wenfang Chen
Reg. No. 52,729